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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,787	12/12/2003	Thierry Canton	FRAV2002/0036 US NP	3482

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/26/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/26/2007.

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Office Action Summary	Application No.	Applicant(s)	
	10/734,787	CANTON ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-22 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-22 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 1/4/2007 has been received, entered and carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 1-18 and 23-24 have been canceled.

2. Claims 21-22 and 27-28 have been amended.

3. Remarks drawn to claim objections and rejections under obviousness-type double patenting, 35 USC 112, first and second paragraphs, 102 and 103.

Claims 19-22, 25-28 are pending in the case.

Claim Objections

The objections to Claims 2, 9 and 11 have been rendered moot by cancellation of the claims. The objection to claim 21 has been overcome by amendment.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of Claims 1-3, 8-12, 15, 17-18 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7,019,023 ('023 patent); claims 1-3 of U.S. Patent No. 6,642,269 ('269 patent); claims 1-7, 9-15 of U.S. Patent No. 6,387,944 ('944 patent); claims 1-5, 11-12, 19-21, 23, 25, 27 and 29 of U.S. Patent No. 6,221,897 ('897 patent); claim 1 of U.S. Patent No. 6,107,494 ('494 patent) has been rendered moot by cancellation of claims 1-18.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-18 under 35 USC 112, first paragraph for lack of enablement has been rendered moot by cancellation of claims 1-18.

Rejection of claims 19-22 and 25-28 for lack of enablement was inadvertently missed in the previous office action. The following new rejection is made of record.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-22 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Alzheimer's disease using the compound of formula IA and for compositions comprising compounds of formula IA and statins (HMG-C0A reductase inhibitors) and ezetimibe (cholesterol reductase inhibitor), does not reasonably provide enablement for the said prevention Alzheimer's using the compounds of instantly claimed and treatment and prevention of Alzheimer's using a combination of the compounds as instantly claimed and all other inhibitors that fall under the broad categories recited in claim 27. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The level of one of ordinary skill
(C) The amount of direction provided by the inventor
(D) The existence of working examples
(E) The level of predictability in the art
(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Instant claim 19 is drawn to prevention of Alzheimer's disease comprising administration of an effective amount of a compound having a hypochloesterolemic activity. The recitation in claim 27, namely a composition comprising a biliary acid reuptake inhibitor and one or more compounds chosen from various other general classes of inhibitors is a broad recitation. The

agents recited are also seen to reasonably include not only known compounds but also unknown compounds as of the filing date. Prevention" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Any therapy which merely reduces the number or severity of symptoms, or which is effective for a period shorter than the subject's remaining lifespan, is considered to be ineffective at preventing a disorder. The term prevention in claim 19 is seen to include the administration of the said compounds and inhibitors to a healthy mammal, and subsequent exposure to conditions that would cause the said disease/condition, wherein the said compounds prevent said exposure from manifesting itself in said mammal so exposed.

The level of one of ordinary skill in the art

The skilled artisan in this field is that of an MD.

The amount of direction provided by the inventor

In the instant case the general class of compounds recited in the instant claims is purely a functional distinction that reads on any known or unknown compounds that might have the recited functions. The specification (page 9) recites broad categories of compounds that may be used in the instant composition and method of treatment. The CAFC further clearly states "A written description of an invention requires a precise definition, such as by structural formula or chemical name, of the claimed subject matter sufficient to distinguish it from other materials. One skilled in the art therefore cannot visualize or recognize the identity of the members of the genus.

The existence of working examples

The working examples set forth in the instant specification are drawn to administration of compound of formula IA to transgenic mice and assaying beta amyloid peptide from the brain extracts. One of ordinary skill in the art will not extrapolate this to compositions comprising all other biliary acid reuptake inhibitors and one or more compounds chosen from various other general classes of inhibitors and to methods of treatment and prevention using the same since the examples provided are not representative of all of the therapeutic agents or combinations encompassed by the recitation of instant claims.

The level of Predictability in the Art

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427.2d 833, 166 USPQ (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since on of skill in the art cannot fully visualize or recognize the identity of the members of the genus. In the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having the claimed functional properties in the combinations/compositions herein. Goodman and Gilman's "The Pharmacological Basis of Therapeutics", 10th Ed., 1996, page 54, teaches that the frequency of significant beneficial or adverse drug interactions is unknown (bottom of the left column at page 54). Relatively small changes in the drug level can have significant adverse consequences. In the instant case one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with the many combinations of any compounds having the functional properties in

the pharmaceutical combinations/compositions claimed herein. Thus, the teachings of Gillman and Goodman clearly support that the instantly claimed invention is highly unpredictable.

In general, preventing disorders according to the definition of prevention given above under the heading "breadth of the claims" is not possible as any so-called preventative effects of a drug therapy are expected to cease when the drug is cleared from the patient's system. More generally, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective. According to Kedar (J. Postgrad Med., 2003, 49, 236-245), no preventive treatment strategies are available for Alzheimer's disease (page 236, left column, lines 5-7). Hence, prevention is also highly unpredictable.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to represent all the combinations/compositions and the method of treatment or prevention encompassed by the recitation of the instant claims. One of ordinary skill in the art would have to carry out undue experimentation to practice the instant invention. Since any structural variation to a compound would be reasonably expected to alter is properties, one of ordinary skill in the art would be required to perform undue experimentation to determine which, if any, of the biliary acid reuptake inhibitors and all of the general classes of inhibitors recites would be useful to make a composition and the efficacy of the same in the said method of treatment and prevention.

Applicants have traversed the rejection advanced earlier by arguing that:

1. Instant claim 27 recites a combination of the compounds of the invention and four classes of inhibitors. According to applicants' enablement is acknowledged by the Examiner for statins (HMG-CoA reductase inhibitors) and ezetimibe (cholesterol uptake or absorption inhibitor). Hence, the objection is only for cholesterol synthesis inhibitors and γ and β APP secretase inhibitors.

2. Regarding the use of secretase inhibitors, applicants refer to the article of Josien, H. Curr. Opin. Drug Discov. Develop., 2002, 5(4), 513-25. According to applicants the use of inhibitors of gamma-secretase, a key enzyme in the production of A beta is currently undergoing preclinical and clinical evaluation and this disclosure of Josien is evidence that gamma and beta APP secretase inhibitors are useful in treating Alzheimer's disease.

Applicants' arguments are not found to be persuasive.

First, it is respectfully pointed out that a copy of the reference, Josien, H., Curr. Opin. Drug Discov. Develop., 2002, 5(4), 513-25, has not been provided by the applicant's for the Examiner's review. Hence, the Examines has considered the statement of Josien as quoted by the applicants in their remarks (at pages 8-9).

Even though enablement exists for statins and ezetimibe, these are specific compounds and the enablement seen for these specific compounds cannot be extrapolated to any and all inhibitors of the respective class of inhibitors as a whole, since these are not representative of the entire class of the respective inhibitors. This also applies to the cholesterol synthesis inhibitors and γ and β APP secretase inhibitors. Instant claim 27 still recites the term prevention

for which a lack of enablement was advanced in the previous office action. The rejection has not been addressed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 2, 3, 8-12 and 17 have been rendered moot by cancellation of the said claims.

The rejection of Claims 21, 22, 27 and 28 has been overcome by amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claims 1-3, 6-12 and 15-18 under 35 U.S.C. 102(b) as being anticipated by Frick et al (US 6,221,897) has been rendered moot by cancellation of the said claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claims 8-12 and 15-18 under 35 U.S.C. 103(a) as being unpatentable over Frick et al (US 6,221,897) and Castaner et al (Drugs of the Future, 2000, 25(7), 679-685) has been rendered moot by cancellation of the said claims.

The rejection of Claims 19-22 and 25-28 under 35 U.S.C. 103(a) as being unpatentable over Frick et al (US 6,221,897) in combination with Refolo et al (Neurobiology of Diseases, 2001, 8, 890-899) is being maintained for reasons of record.

Applicants have traversed the rejection by arguing that:

1. Frick et al disclose compounds of formula IA but do not teach or suggest the use of the said compounds for the treatment of Alzheimer's disease.

2. Refolo discloses that cholesterol could play a major role in the pathogenesis of Alzheimer's but do not teach the use of compounds of instant formula IA for treating Alzheimer's. Refolo teaches statins and compounds that inhibit HMG-CoA reductase for the treatment of Alzheimer's. Refolo's compound is blood-brain permeable and the compounds of the instant invention are not, even after oral administration.

Applicants' arguments are not found to be persuasive.

According to Refolo et al studies have shown that cholesterol may play an important role in the pathogenesis of Alzheimer's disease. A strong correlation between the amount of plasma cholesterol level and brain A-beta peptides and beta-amyloid was observed (page 890, abstract). These amyloid peptides are present in the neurite plaque of Alzheimer's patients (page 890, Introduction). According to Refolo's disclosure then, a compound that reduces cholesterol level can be used for treatment of Alzheimer's. Fricke's compounds, which are the same as

compounds of instant formula IA, are useful for lowering cholesterol levels. Whether the active agent reduces the cholesterol level by blood-brain barrier permeation or otherwise is not relevant.

Hence, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat Alzheimer's disease in a patient by administering a compound of instant formula IA since it is known in the art that compounds of instant formula IA have hypochloesterolemic activity according to Fricke et al and cholesterol lowering drugs are shown to reduce beta-amyloid peptides that play a role in the pathogenesis of Alzheimer's disease.

One of ordinary skill in the art would be motivated to use compounds of instant formula IA in a method as instantly claimed in order to look for other more efficient hypochloesterolemic compounds. The skilled artisan would expect other hypochloesterolemic agents to work since reduction of cholesterol levels is associated with reduced amyloid peptides.

Conclusion

Claims 19-22 and 25-28 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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